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Application Number	09/887,933
Filing Date	June 22, 2001
First Named Inventor	Robert P. HOF
Group Art Unit	1621
Examiner Name	S. Kumar
Total Number of Pages in This Submission: 40	Attorney Docket Number: **246152014800**

ENCLOSURES (*check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
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  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
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  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual Name	MORRISON & FOERSTER LLP Carolyn A. Favorito - 39,183
Signature	
Date	June 9, 2003

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PATENT
Docket No. 246152014800

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the application of:

Robert Patrick HOF *et al.*

Serial No.: 09/887,933

Filing Date: 22 June 2001

For: PROCESS FOR RACEMISING AN ENANTIOMER-ENRICHED SCHIFF BASE OF AN AMINO ACID AMIDE

Examiner: S. Kumar

Group Art Unit: 1621

#18
9/17/03

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is in response to the Notification of Non-Compliance with 37 C.F.R. 1.192(c) mailed May 8, 2003, thus setting a date for response of June 8, 2003. In accordance with 37 C.F.R. § 1.192, this Brief, along with the Appendix, is filed **in triplicate** and is accompanied by the required fee.

sd-148385

1. Real Party in Interest

The real party in interest in this appeal is DSM N.V. by virtue of an assignment recorded in the U.S. Patent and Trademark Office on 22 June 2001, Reel/Frame: 011952/0327.

2. Related Appeals and Interferences

There are no other Appeals or Interferences known to the appellants, the appellants' legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the present pending appeal.

3. Status of Claims

Claims 1-11 were contained in the original specification and were cancelled and replaced with claims 12-22 filed concurrently in a Preliminary Amendment. Pending claims 12-22 have been finally rejected. The claims involved in this appeal, claims 12-22, are presented in the Appendix attached hereto as Exhibit A.

4. Status of Amendments

Claims 12 and 22 were amended in the Amendment under 37 C.F.R. § 1.111, filed 19 April 2002, and Claim 12 was amended further in the Amendment under 37 C.F.R. § 1.116, filed 24 October 2002, which amendment has been entered according to the Advisory Action mailed 7 November 2002.

5. Summary of the Invention

The invention is directed to an improved process of more quickly and efficiently racemizing an enantiomer-enriched Schiff base of a primary amino acid amide in comparison to conventional processes, while substantially reducing the extent that byproducts are formed. Please see the present specification on page 1, lines 18-20. The process requires the use of a

strong base in an organic solvent, wherein the strong base is chemically reactive with water. The invention also requires the use of a Schiff base of a primary amino acid amide. A *primary* amino acid amide is an amino acid amide where the amide-NH_2 is unsubstituted, that is, there are 2 hydrogen atoms attached to the N. Please see the present specification on page 1, lines 21-22. In contrast, a skilled artisan would understand that in the case of *secondary* amino acid amides, one of the hydrogen atoms on the N is replaced with a non-hydrogen moiety.

6. **Issues**

A) Whether an organic chemistry textbook excerpt relating to background information and stereochemistry contains "new issues presented for review" as alleged in the Notification of Non-Compliance mailed May 8, 2003.

B) Whether *prima facie* obviousness under 35 U.S.C. § 103 has been established for claims 12-22 based on U.S. Patent No. 5,674,857 issued to Hijiya *et al.* (Hijiya), where Hijiya does not provide motivation to substitute its secondary amino acid amides for the claimed primary amino acid amides, as there is no teaching or suggestion of a primary amino acid amide in Hijiya nor expectation that such substitution will be equivalent or successful.

7. **Grouping of Claims**

The claims stand or fall together.

8. **Argument**

A) No New Issue Presented on Appeal

The Examiner had alleged that the "Appeal Brief filed on Apr 21, 2003 is defective for failure to comply with one or more provisions of 37 CFR 1.192(c). See MPEP § 1206." Further

the Examiner has explained that the "brief has raised new issues by submitting a new evidence by the way of citing a reference." Moreover the Examiner indicated that, "[t]he brief contains new issues presented for review. The appellants have submitted new evidence in the form of a new reference, which is not cited earlier. See CFR. 1.116 and CFR 1.195. See page 5 of the brief."

The "evidence" to which the Examiner objected on page 5 of the Brief relates to an excerpt from an organic chemistry textbook that represents what is known by one or ordinary skill in the art. Specifically, aside from a general discussion on stereochemistry, chirality and optical activity, the textbook excerpt emphasizes what is known in the art, namely that enantiomers and diastereomers differ in that enantiomers are identical in all physical properties except their signs of optical rotation, whereas diastereomers have different physical and chemical characteristics. This excerpt presented nothing new to the Examiner that was not found in the reference cited by the Examiner; Hijiya exemplified this definition by disclosing in column 1, lines 66-67 thereof that the "D" diastereomer crystallizes out of the liquid that contains the "L" diastereomer.

With regard to the noncompliance of the requirements of 37 C.F.R. § 1.192(c), MPEP § 1206 states:

> 37 CFR 1.192(c) merely specifies the minimum requirements for a brief, and does not prohibit the inclusion of other material which an appellant may consider necessary or desirable, for example, a list of references, table of content, table of cases, etc. A brief is in compliance with 37 CFR 1.192(c) as long as it includes items (1) to (9) in the order set forth (with the appendix, item (9), at the end).

Thus it is not clear to appellants which provision of 37 C.F.R. § 1.192(c) is defective as all of the sections are set forth in the Appeal Brief filed April 9, 2003 as required by this rule.

The Examiner has also referred to 37 C.F.R. § 1.195 and has alleged that the Brief contains "new issues presented for review." However, 37 C.F.R. § 1.195 appears to be directed to affidavits or declarations or presumably similar exhibits after appeal. Specifically, the section states, "affidavits, declarations, or exhibits submitted after the case has been appealed will not be admitted without a showing of good and sufficient reasons why they were not earlier presented." It is respectfully submitted that a textbook excerpt which illustrates that which is known in the art does not present a new issue, nor does it rise to the level of an affidavit or a declaration or a similar exhibit that perhaps may provide evidence to swear behind a reference, or perhaps evidence of advantageous results. Indeed, the Examiner has not indicated what new issue has been raised.

Appellants' counsel has attempted to telephone the Examiner and the Examiner's supervisor Johann Richter, but both were out of the Office until after the due date for the Reply to the Notice of Non-Compliance. Appellants' counsel has contacted Examiner Bart, whose name was left on Examiner Richter's out of office voicemail message. However, Examiner Bart indicated that the excerpts submitted by appellants may be classified as raising a new issue and such noncompliance is made at the discretion of the Examiner. It is respectfully submitted that such a response is inadequate. It is respectfully submitted that the Examiner either specify the new issue that is presented for review or consider what is known in the art while considering the issues on appeal.

Even if for the sake of argument, the excerpt of the organic chemistry textbook did rise to the level of evidence included in an affidavit, declaration or exhibit, 37 C.F.R. § 1.195 allows admission of such submission with the showing of good and sufficient reasons why they were

not earlier presented. It is respectfully submitted that such good and sufficient reasons were submitted on page 5 of the Appeal Brief filed April 9, 2003. Particularly, appellants have pointed out that a skilled artisan would understand that a compound that contains two chiral centers forms two diastereomers which have different chemical and physical properties, a fact which may have escaped the attention of the Examiner when applying the Hijiya reference to the present claims. Thus, it is respectfully submitted that pointing out what is known in the art is good and sufficient reason why this particular excerpt was submitted at this time since the appellants respectfully submit that such an understanding should have been used to determine the applicability of the Hijiya reference, but ostensibly was not.

Nonetheless, the appellants have not included the offending excerpt as an attachment to the present Appeal Brief but have rather quoted the pertinent section as a footnote with regard to diastereomers having different chemical and physical properties. Thus, the Examiner or the Board may reference this textbook that includes such reference to that which is understood by an ordinary artisan or, if more convenient, the excerpt attached to the Appeal Brief previously filed on April 9, 2003.

B) Hijiya Does Not Render Obvious the Present Claims.

1) **Hijiya Does Not Disclose All Claim Limitations**

In order to establish a *prima facie* case of obviousness it is necessary that all of the claim limitations are found in the cited reference. Please see MPEP §2143.03. There is no teaching or suggestion in Hijiya of the racemization of a Schiff base of a *primary* amide of an amino acid. As can be seen in Hijiya's Schiff base of an amino acid amide, *i.e.*, formula (2) or (3), that is reacted with a base, none of the nitrogen atoms are linked to two hydrogen atoms as is required

by definition in a primary amino acid amide, but rather are linked to only one hydrogen atom and thus are by definition secondary amino acid amides. The statement of the rejection in the final Office action appears to acknowledge this fact (see page 3, third paragraph, of the final Office action mailed July 9, 2002).

Although such lack of teaching or suggestion is sufficient to establish that a *prima facie* case of obviousness has not been established, there are additional reasons as outlined below as to why a *prima facie* case has not been established.

2) Hijiya Does Not Teach Selection of Primary Amide for Which a Successful Racemization Process is Expected

Other elements needed to establish *prima facie* obviousness are that there must be a suggestion or motivation to modify the reference to arrive at the claimed invention and that there must be a reasonable expectation that such a modification would be successful. Please see MPEP § 2143. Hijiya does not teach or suggest the racemization of Schiff bases of primary amides in general and provides no suggestion or motivation to modify the secondary amino acid amides disclosed therein to arrive at the primary amino acid amides used in the claimed invention. Even if for the sake of argument Hijiya teaches a genus of amino acid amides, there is no indication that selection of one species of such a genus of amides, namely a primary amino acid amide, would reasonably be expected to be successful. Nowhere in Hijiya is it suggested that reacting a base as claimed with a Schiff base of a primary amino acid amide would result in a faster racemization process in comparison to conventional processes. Please see the present specification, for example, page 1, lines 9-31. Rather, Hijiya's stated objective is to use low cost starting materials to make one subset of secondary amino acid amides, namely D-amino acid-N-(S)-α-alkylbenzylamides. Please see Hijiya, column 1, line 58 and column 3, lines 39-43. As

such, the two remaining elements necessary for establishing *prima facie* obviousness have not been shown.

3) Hijiya Does Not Suggest that a Primary Amide Would Function Equivalently as a Secondary Amide Nor is Hijiya's Process Directed to the Same Problem as the Claimed Invention

Additionally, it is respectfully submitted that there is no indication of why a skilled artisan would expect that a *primary* amide of an amino acid would function equivalently in the teachings of Hijiya. Hijiya's secondary amide of an amino acid has two chiral centers (one at the amino acid's alpha carbon, which is labeled with an asterisk in any of figures (1), (2) or (3), and the second at the carbon to which R_2 is attached) which permits the formation of two diastereomers. A skilled artisan would understand that a compound that contains two chiral centers form two diastereomers which have different chemical and physical properties. Such different properties result because the diastereomers are not mirror images of each other.[1] This phenomenon is illustrated by the fact that Hijiya's "D" diastereomer crystallizes out of the liquid that contains the "L" diastereomer. Please see column 1, lines 66-67 of Hijiya. Such crystallization facilitates the conversion and isolation of the "D" stereoisomer and, upon hydrolization thereof, is converted to the "D" version of the starting material that has the opposite chirality of the "L" starting material. Such isolation is in contrast to racemization *per se,* which is defined in the specification as lowering the enantiomeric excess of enantiomer-enriched compounds. See Hijiya column 2, lines 6-33, and the present specification on page 2,

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[1] Please see Stanley H. Pine *et al.*, *Organic Chemistry*, 120 (1980) which states:
Whereas enantiomers are identical in all physical properties except their signs of optical rotation, diastereomers have different physical and chemical characteristics.

lines 4-5. For example, if the enantiomeric excess is lowered to 0, then a racemate is present (*i.e.,* equal amounts of each mirror image enantiomer). As such, the present invention does not rely on the phenomenon described in Hijiya and is directed to a different problem in the art.

Moreover, the above teachings of Hijiya *cannot* be performed by preparation of a primary amide in place of the secondary amide because the resulting primary amide of an amino acid would only have a single chiral center at the alpha carbon. Racemization at that center would create two enantiomers that cannot be separated by the method disclosed in Hijiya. Pine, *supra*, at 117-118. Therefore, appellants respectfully submit that there is *no* expectation of success in the asserted modification of Hijiya to utilize a primary amide (see the basis of the requirement at MPEP 2143.02 and the cases cited therein). To the contrary, there is evidence that the teachings of Hijiya would lead the artisan of ordinary skill *away from* the use of a primary amide and toward the use of a secondary or tertiary amide because only secondary or tertiary amides can introduce a second chiral center into the resulting amide.

4) Hijiya Does Not Point to Particular Bases that are Required in Claimed Invention

It is respectfully submitted that there must be more than mere disclosure of a species (*i.e.,* a base reactive with water) to provide the motivation to combine such disclosure with another species (*i.e.,* primary amino acid amide, albeit not disclosed in Hijiya) even where the reference discloses the genus. *In re Baird*, 16 F.3d 380, 29 US.P.Q.2d (BNA) 1550 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 21 US.P.Q.2d (BNA) 1941, 1944 (Fed. Cir. 1992). There is no recognition in Hijiya of the necessity to use the species of a base reactive with water. Any of the bases disclosed in column 4, lines 1-6 of Hijiya may be used in the process, and thus a skilled person

would not be lead to only those bases that are reactive with water. Thus, there is insufficient motivation to select the particular species of base used in the claimed invention.

5) Motivation Provided in Advisory Action is Insufficient

The asserted motivation set forth in the Advisory Action is misplaced, namely "Inasmuch as there is [a] chiral center, there is motivation to use the process of Hijiya et al for primary amide racemization." As discussed above, more than simply the presence of chiral center is needed to arrive at the claimed method, that is, motivation to select a primary amides and motivation to select the type of base expected to be successful is needed. Regardless of motivation, all of the claim limitations must be present as well as an expectation of success. As such, not a single element necessary for establishing *prima facie* obviousness has been appropriately established.

9. Appendix

An Appendix containing a copy of the claims as currently pending is attached.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to Deposit Account No. 03-1952.

Respectfully submitted,

Dated: June 9, 2003 By: _____

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APPENDIX

12. A process for racemising an enantiomer-enriched Schiff base of a primary amide of an amino acid which process comprises contacting said enantiomer-enriched Schiff base of a primary amide of an amino acid with a strong base in an organic solvent,

wherein said strong base is chemically reactive with water.

13. The process of claim 12 wherein the strong base is a metal alkoxide, a metal alkyl, a metal amide, or a metal hydride.

14. The process of claim 13 wherein the strong base is a metal alkoxide.

15. The process of claim 12 wherein the strong base is present in an amount of 0.001-1000 mole% relative to the enantiomer-enriched Schiff base.

16. The process of claim 15 wherein the strong base is present in an amount of 0.1-100 mole% relative to the enantiomer-enriched Schiff base.

17. The process of claim 12 wherein the enantiomer-enriched Schiff base is an N-benzylidene primary amino acid amide.

18. The process of claim 12 wherein the enantiomer-enriched Schiff base is derived from an aliphatic primary amino acid amide.

19. The process of claim 18 wherein the enantiomer-enriched Schiff base is derived from tertiary-leucine amide.

20. The process of claim 12 wherein the organic solvent is an aromatic hydrocarbon, a cyclic aliphatic hydrocarbon or an ether.

21. The process of claim 20 wherein the organic solvent is an aromatic hydrocarbon.

22. The process of claim 12 wherein said enantiomer-enriched Schiff base has been prepared from the primary amide of the amino acid in said organic solvent.